REMARKS

First, Applicant would like to thank the Examiner for the fruitful Interview conducted on January 23, 2002 with Paul Fehlner and the undersigned. Applicant believes that several issues pertaining to the patentability of the pending claims were resolved, and appreciate the Examiner's suggestions on claim amendments.

This submission is in response to the Office Action dated January 2, 2002. Claims 13 and 14 have been canceled, without prejudice or disclaimer. Claim 5 has been amended. Claims 2-3, 5-10, 12-13, 15-17, and 25-26 are pending. Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

Claim 5 has been amended to recite that the patient is not sensitized to the hapten prior to administering of the composition. As discussed during the interview and in greater detail below, the modifications to the then existing immunotherapy protocol (e.g., as described in Berd 1991, Berd 1994, and Berd '551) that lead to an enhanced response are (1) administration of a single dose of cyclophosphamide and (2) omitting a hapten-specific presensitization step. Omitting the presensitization step, in particular, led to improved patient responses, which was surprising given that one would expect presensitization to hapten to enhance immunity to haptenized tumor cells. These amendments are supported by the specification at page 53, first and second paragraphs. In particular, the amendment is supported at

page 53, lines 9-10. Claim 5 has also been amended to correct a typographical error in the spelling of "cyclophosphamide" and to correct grammatical errors.

Claim Objections

The Examiner has objected to claim 5 for a typographical error in the spelling of the term "cyclophosphamide". With this amendment, the typographical error has been corrected, obviating this rejection.

The Examiner has objected to claim 11 for depending from a canceled claim. Since claim 11 was canceled, without prejudice or disclaimer, in the amendment filed February 1, 2000, this objection is moot.

Non-Obviousness of the Invention

The Examiner has maintained the rejection of all claims under the judicially created doctrine of Obviousness-Type Double Patenting over claims 1 and 2 of U.S. Patent No. 5,290,551 to Berd (hereinafter Berd '551), in view of U.S. Patent No. 5,478,556 to Elliot (hereinafter "Elliot"), or Mankiewicz et al. (Cancer Immunol Immunother 1977;2:27-39; hereinafter "Mankiewicz"), or Humphrey et al. (Surg Oncol Gynecol Obstr 1971;March: 437-442; hereinafter "Humphrey").

The Examiner has also maintained the rejection of all claims under 35 U.S.C. §103(a) over Berd '551, or Berd et al. (Cancer Res 1991;51:2731-2734;

hereinafter "Berd 1991"), or Berd et al. (Proc Am Assoc Cancer Res 1994;35:667-668; hereinafter "Berd 1994"), in view of Elliot, or Mankiewicz, or Humphrey.

In response, Applicant has further amended the independent claim to particularly point out and distinctly claim the invention. Claim 5 and claims dependent thereon, are now directed to a method of administering to a patient a haptenized tumor cell composition at weekly intervals, wherein cyclophosphamide is only administered before the first dose, and wherein the patient is not pre-sensitized to the hapten. Applicant has found that this unique administration schedule yields a surprisingly effective anti-tumor response in patients.

As shown in Example 15 (pp. 52-53 of the specification), administration of vaccine, without presensitization to the hapten, DNP, and with cyclophosphamide only administered before the first vaccine dose, yielded a DTH response in 16/27 patients, corresponding to 59% of the patients in this group. All other schedules, whether utilizing hapten presensitization followed by monthly vaccine injections, weekly injections with occasional cyclophosphamide administrations, or weekly administrations alternating between haptenized and non-haptenized vaccine, resulted in lower response rates. Thus, as established during the interview, the combination of parameters set forth by the current claims represents a novel administration regimen that leads to an unexpectedly effective anti-tumor response.

None of the references cited by the Examiner teaches or suggest such a administration regimen, or its benefits. Since pre-sensitization to hapten is limited to

studies actually employing a hapten, Elliot, Mankiewicz, and Humphrey cannot be but silent on this issue. The Berd '551 patent and Berd 1991 unequivocally teach pre-sensitization to hapten, followed by monthly injections of vaccine wherein each vaccine injection is preceded by a dose of cyclophosphamide. Berd 1994 also employs monthly administration of vaccine, wherein at least the first two vaccine dosages are preceded by cyclophosphamide, and does not disclose or imply that excluding pre-sentsitization would enhance the anti-tumor response. On the contrary, Berd 1994 expressly refers to the protocol of Berd 1991:

> In our study involving patients with surgically-incurable metastic melanoma (7) [Berd, D., et al., Cancer Res., 51:2731-2734, 1991.] the vaccine was administered every 28 days and low dose cyclophosphamide was given three days before each vaccine injection.

In describing the new experimental data, Berd 1994 reports:

> We treated 36 patients...They received eight injections of DNP-vaccine at four-week intervals; cyclophosphamide was administered three days before the first two-vaccines only.

Apparently, then, the only specified difference between Berd 1994 and Berd 1991 was the cyclophosphamide regimen. Berd 1991 expressly included a presensitization step; Berd 1994 implicitly does as well.

These references, taken alone or in any combination, therefore fail to suggest the exclusion of pre-sensitization; they also fail to provide any expectation of success for such a procedure. Furthermore, none of these references suggest a weekly dosage schedule in combination with omitting presensitization and a single

dose of cyclophosphamide. The surprising success of the specific administration design of the invention in evoking an anti-tumor response was achieved by Applicant, as described in the present disclosure. Accordingly, the instant invention is not obvious over the references cited by the Examiner.

With respect to claim 26, the following statement was made in the Office Action, pertaining to Berd '551 (pages 3 and 5-6), and Berd 1991 (page 6-7) in support of the obviousness rejections:

> A dosage including 10×10^6 tumor cells was used, which is at least 10^6 tumor cells per dose....While the method does not explicitly recite a maximum does of 7.5×10^6 cells per dose, this specific dose would be an obvious variation of the instant methods, encompassed by art known techniques of dosage optimization.

This reasoning does not take into consideration that in both Berd '551 and Berd 1991, cell dosages in the range of 10×10^6 to 25×10^6 cells per dose were administered to the patients (Examples 1-3 of Berd '551; page 2731, 2nd col., 1st full paragraph of Berd 1991). Based on these references, one of skill in the art would therefore have assumed that any optimum administration range lay within this range. Indeed, the results set forth in the present claims represent a surprising discovery, namely that a lower dosage wholly outside of the range disclosed in the prior art references could induce a similarly positive immune response. In the field of immunotherapy using autologous cells, this result is not only surprising, but also

important from the standpoint of having enough autologous cells from the patient, usually via surgery, to produce a more effective number of dosages of the vaccine.

As discussed during the interview, the success of the present invention stems from the claimed features, *i.e.*, a single dose of cyclophosphamide, and no pre-sensitization. The dosing schedule, while of less importance, also impacts patentability. Thus, the Examiner concerns that the "...claims are drawn to a broad range of possible dosage variants, including numerous CY dosage variants, any number or absence of adjuvants, etc." are obviated.[1]

Finally, Applicant would like to address the issue raised by the Examiner, in the last paragraph, on page 11of the Office Action:

> The declaration and the post-filing evidence clearly states that it is the single administration of cyclophosphamide administration, in combination with an induction dose of vaccine and then weekly administration which achieves unexpected results.

The Rule 132 Declaration that was filed in this application on December 12, 2001, sought to explain the unpredictability in the art of immunotherapy by exemplifying another parameter which has been shown to yield a surprisingly pronounced anti-tumor response, namely an induction dose of haptenized tumor cells.[2] The added effect of an induction dose had not been recognized at the time of the filing

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[1] One point in particular bears mention. Contrary to the "absence of adjuvants" statement, Claim 5 recites administration of the vaccine with an adjuvant.

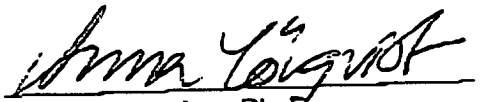
[2] This discovery is the subject of another, co-pending patent application filed by Applicant.

of the instant application. However, whether an induction dose could be used or not does not change the invention disclosed in the present application, which is that vaccine administration, preceded only by one injection of cyclophosphamide and excluding pre-sensitization, and preferably on a weekly basis, leads to a surprisingly effective anti-tumor response.

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



Anna Lövqvist, Ph.D.
Limited Recognition Under 37 C.F.R. §10.9(b) (see attached)
Representative for Applicant

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PATENT TRADEMARK OFFICE

Docket No: 1225/1E251US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: David Berd

Serial No.: 09/304,859 Art Unit: 1642

Confirmation No.: 1252

Filed: May 4, 1999 Examiner: J. Hunt

For: **COMPOSITION COMPRISING TUMOR CELL AND EXTRACTS AND METHOD OF USING THEREOF**

MARK-UP FOR RESPONSE TO OFFICIAL ACTION

March 6, 2002

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

IN THE CLAIMS:

Please amend claim 5 pursuant to 37 C.F.R. 1.121 as follows:

5. (Twice amended) A method for inducing an anti-tumor response in a mammalian patient suffering from a tumor, which method comprises administering to said patient a composition comprising a tumor cell or tumor cell extract with an adjuvant, wherein the tumor cell or tumor cell extract is:

(i) conjugated to a hapten;

(ii) of the same tumor type as the patient's tumor;

(iii) not allogeneic to said patient; and

(iv) incapable of growing in the body of the patient after injection; [,]

and repeating said administration at weekly intervals,

wherein a therapeutically effective amount of [cyclophosphamice] cyclophosphamide is administered only prior to the first administration of the composition, wherein the patient is not sensitized to the hapten prior to administration of the composition, and wherein the composition, when administered with the adjuvant, elicits an anti-tumor response.

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PATENT TRADEMARK OFFICE

Docket No: 1225/1E251US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: David BERD

Serial No.: 09/304,859 Art Unit: 1642

Confirmation No.: 1252

Filed: May 4, 1999 Examiner: J. Hunt

For: **COMPOSITION COMPRISING TUMOR CELL AND EXTRACTS AND METHODS OF USING THEREOF**

EXAMINER'S COURTESY COPY OF PENDING CLAIMS

March 11, 2002

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

2. (Amended) The method of claim 5, wherein said composition is administered for at least three times.

3. (Amended) The method of claim 5, wherein said composition is administered for at least six times.

5. (Twice amended) A method for inducing an anti-tumor response in a mammalian patient suffering from a tumor, which method comprises administering to said patient a composition comprising a tumor cell or tumor cell extract with an adjuvant, wherein the tumor cell or tumor cell extract is:

(i) conjugated to a hapten;

(ii) of the same tumor type as the patient's tumor;

(iii) not allogeneic to said patient; and

(iv) incapable of growing in the body of the patient after injection;

and repeating said administration at weekly intervals,

wherein a therapeutically effective amount of cyclophosphamide is administered only prior to the first administration of the composition, wherein the patient is not sensitized to the hapten prior to administration of the composition, and wherein the composition, when administered with the adjuvant, elicits an anti-tumor response.

6. (Amended) The method of claim 5 wherein said therapeutically effective amount of cyclophosphamide comprises administering a dose of about 300 mg/M^2 of cyclophosphamide.

7. (Amended) The method of claim 5 wherein said tumor cell or extract is selected from the group consisting of melanoma, lung, colon, breast, kidney, prostate, ovarian and leukemia tumor cell or extract.

8. The method of claim 7, wherein said tumor cell or extract is a melanoma tumor cell or extract.

9. (Amended) The method of claim 5 wherein said hapten is selected from the group consisting of dinitrophenyl, trinitrophenyl, N-iodoacetyl-N'-(5-sulfonic 1-naphthyl) ethylene diamine, trinitrobenzenesulfonic acid, fluorescein isothiocyanate, arsenic acid benzene isothiocyanate, trinitrobenzenesulfonic acid, sulfanilic acid, arsanilic acid, dinitrobenzene-S-mustard and combinations thereof.

10. The method of claim 9 wherein said hapten is dinitrophenyl.

12. (Amended) The method of claim 5 wherein said adjuvant is selected from the group consisting of Bacillus Calmette-Guerin, QS-21, detoxified endotoxin and a cytokine.

15. (Amended) The method of claim 5 wherein said mammalian patient is a human.

16. (Twice amended) The method of claim 5 wherein said composition comprises at least 10^6 tumor cells or cell equivalents extract per dose.

17. (Amended) The method of claim 5 wherein said anti-tumor response is at least one of the following: tumor necrosis, tumor regression, tumor inflammation, tumor infiltration by activated T lymphocytes, stable disease and prolongation of patient survival.

25. (New) The method of claim 5, wherein the cyclophosphamide is administered 3 days prior to administration of the composition.

26. (New) The method of claim 5, wherein the composition comprises a maximum of 7.5×10^6 cells or cell equivalents per dose.

BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
UNITED STATES PATENT AND TRADEMARK OFFICE

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Expires: July 12, 2002

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